“New Approaches Towards The Synthesis Of Fused Heterocyclic Compounds And Screening Of Their Biological Activities”

SHORT RESUME OF THE PLAN PROPOSED FOR INVESTIGATION FOR Ph.D. DEGREE UNDER THE FACULTY OF SCIENCE.

To be submitted to

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1. Introduction:

Heterocyclic compounds are organic compounds with a ring structure that contains in the cycle at least one carbon atom and at least one other than carbon atom, such as N, O, or S. The most common cycles contain five or six atoms, with the stability of these rings being higher than that of three, four, seven, or larger rings. However, many heterocyclic compounds with a different number of atoms than five or six are known. Heterocyclic rings can be either nonaromatic or aromatic. Heterocyclic compounds have a wide range of application. They are predominantly used as pharmaceuticals, as agrochemicals and as veterinary products.

The organic heterocyclic compound like benzimidazole, benzothiazole, pyridine, pyrimidine, thiazins are one of the most important classes of biologically active molecule. Pyrimidine is basic part of DNA and RNA and it is widely distributed in living beings. They possess a wide range of biological properties such as antimicrobial, antibacterial, antifungal, antitumor activities. Many marine natural products having pyrimidines as its core nucleus are used as thyroid drugs.

Some of heterocyclic compounds have great interest both for theoretical as well as practical standpoint. Heterocyclic compound occurs widely in nature and in variety of non – naturally occurring compounds. An enormous number of heterocyclic compounds are known and this number is increasing rapidly. Various compounds such as vitamins, hormones, alkaloids, hemoglobin, antibiotics contain heterocyclic ring system and are essential to life. Also there is large number of heterocyclic compounds which shows an important application in pharmacological and agrochemical field as well as important intermediate in synthesis.

Pyrazoles are one of the most interesting heterocyclic compounds because of their pharmacological, agrochemical, photographic and industrial applications. There are generally fused pyrazoles which are seen to exhibit H.I.V. 1 reverse transcriptase inhibitor activity.

Benzothiazole, pyrazole and its derivatives have been investigated as central muscle relaxants. It has been reported that benzothiazole fused with pyrimidine and pyrazole found to possess wide spectrum of activities like anticonvulsant, antibacterial, anti inflammatory and antifungal.

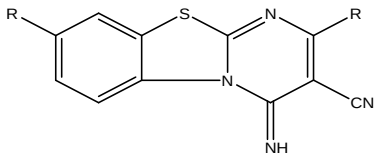
The pyrazole – pyrimidine derivatives have received a great deal of attention due to their pharmacological activity. These compounds display marked antitumor and anticancer activity. While pyrazole–pyrimidine derivatives have demonstrated promising antimicrobial activity against gram positive bacteria.

2. Review of Literature and Development in the subject (Previous work done in the relevant area):

Now we are working on the development of the Nitrogen, Sulphur and oxygen containing fused heterocyclic compounds by applying different methods and using different catalytic reagents or catalysts. Some of them have been mentioned below.

The present work with our research group involves the synthesis of novel biological active fused heterocycles containing imino/oxo pyrimdine ring fused through the nitrogen atom with another biologically active nucleus such as Pyridine, Imidazole, pyrazole, thiazole, benzothiazole, and quinolines which are published in different reputed journals.

- A convenient synthesis of fused imino pyrimido [2,1-b] benzothiazole and its 2-substituted derivatives. ARKIVOC 2006 (X) 190-198 S. V. Kuberkar and et. al[1].



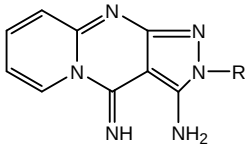
R = a) Different active methylene compounds

b) Different Heteryl amine

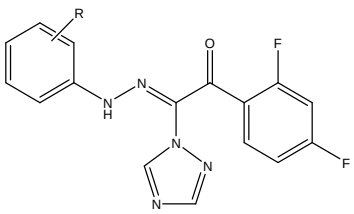
c) Different substituted phenols

d) Different substituted anilines

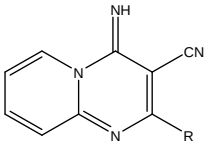
- An efficient synthesis of some novel 3-cyano-4-imino-2-(methylthio)-4H-pyrido[1,2-*a*]pyrimidine and their derivatives, Sambhaji P. Vartale,et al.[2]***J. Heterocyclic Chem*****,** 2013, 50,351-355.



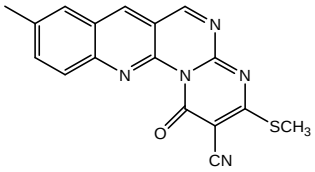
- Synthesis and biological activity of some fluorinated Arylhydrazotriazoles. **Arabian Journal of Chemistry** (2012) 5, 257–261.M.S. Shingare,* S.A. Sadaphal et.al[3].



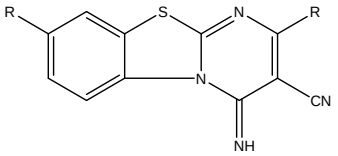
- Synthesis and evaluation of 3-cyano-4-imino-2-methylthio-4H-pyrido [1,2-a] pyrimidine derivatives as potent antioxidant agents. Arabian Journal of Chemistry (2012) xxx, xxx–xxx S.P. Vartale and et.al[4].



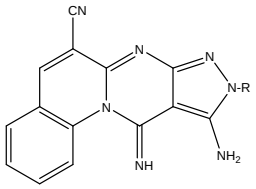
- Convenient one pot synthesis of 3-cyano-9-methylthio-4-oxo-4H-pyrimido[2,1-*b*] quinoline and its reactions with selected nucleophiles, Sambhaji P. Vartale et al.[5] ***Letters in Organic Chemistry***,2009,6(7), 544-548.

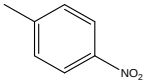
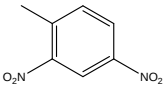
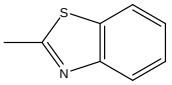
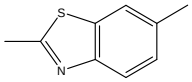


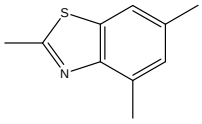
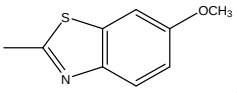
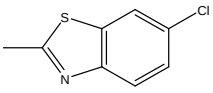
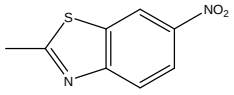
- A convenient synthesis of fused imino pyrimido [2,1-b] benzothiazole and its 2-substituted derivatives **ARKIVOC** 2006 (X) 190-198 S. V. Kuberkar and et. Al[6].



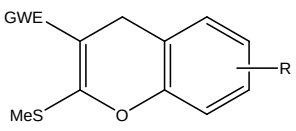
- Synthesis And Antimicrobial Evaluation Of 3-Amino11-Cyano-4- Imino- Pyrazolo [4, 5-E]-*4H*-Pyrimido [2, 1-B] Quinoline And Their Substituted Derivatives. Heteroletter, Vol. 2: (1), 2012, 71-78. ISSN: 2231–3087(print)/ 2230–9632 (Online) Sambhaji P. Vartale and et.al[7].



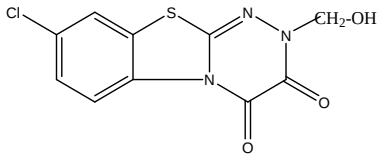
R = -H, ,  ,  ,  , 

 ,  ,  , 

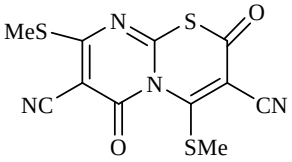
- One-Pot Synthesis of Polyfunctionalized 4H-Chromenes and Dihydrocoumarins Based on Copper(II) Bromide-Catalyzed CC Coupling of Benzylic Alcohols with Ketene Dithioacetals, Qun Liu et.al[8], ***Adv. Synth. Catal.***2010, 352, 1593 – 1599.



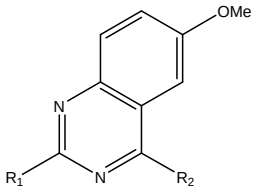
- Synthesis and some novel reactions of 8-chloro-2H-[1,2,4] triazino [3,4-b] [1,3] benzothiazole-3,4-dione and 6-chloro-2-hydroazino-1,3-benzothiazole **Journal of chemical research** 2005 October, 632-635, S. V. Kuberkar and et.al[9].



- Simple and efficient of substituted pyrimido [2,1-b][1,3] thiazines. Heterocyclic communication (2013;19(3): 215-218 Sambhaji P. Vartale *, Shivaji B. Sirsat[10].

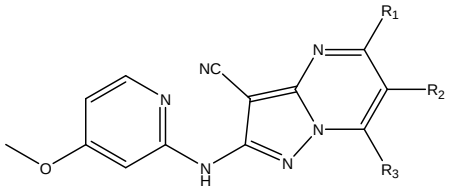


- Synthesis of Densely Substituted pyrimidine Derivatives. JOC note (American chemical society) 2009, 8460-8463. Omar K. Ahmad, and Mohammad Movassaghi* Matthew D. Hill[11].



R_1 = - Ph, -H R_2 = -H, -NH-t-Bu, $-NH_2$, -OH

- Optimization of pyrazolo[1,5-a]pyrimidine based compounds with pyridine scaffold. (Arabian Journal of Chemistry, Science Direct) Volume 15, Issue 8, August 2022, 104015, Mohamed A. Abdelgawad et.al[12].



3. Objectives of Research/ Proposed Hypothesis:

- Synthesis of some catalytic reagents.
- Extending the research of catalytic reagents to new domains, especially targeting the synthesis of different novel imino/oxo fused heterocyclic derivatives.
- Studying mechanistic details and pathways of catalytic reagents like ketene thioacetals.
- Investigate the role of catalytic reagents in the activation of substances.
- Study of synthesis of fused heterocyclic compounds by multi component reaction pathway.

- Synthesize different novel heterocyclic compounds by studying different reactions of prepared catalytic reagents with different organic compounds.
- Establishment of the structure of newly synthesized compounds with help of spectral data.
- Evaluation of physicochemical properties of synthesized novel heterocyclic compounds
- Evaluation of biological properties of synthesized novel heterocyclic compounds.
- Studying Molecular modeling of synthesized compounds.

4. Methodology to be adopted:

- Literature Survey.
- Synthesis and conformation of the structure of catalytic reagents.
- Synthesis and characterization of different heterocyclic derivatives by applying novel catalytic reagents.
- Characterization of newly synthesized heterocyclic compounds such as IR, ^{1}H-NMR, ^{13}C-NMR, Mass Spectroscopy.
- Study of the physicochemical parameter of synthesized compounds.
- Evaluation of microbiological activities of synthesized compounds.
- Submission of data to International /National reputed journals for publication.

5. Importance of study/ Society application:

- **International Status:**

Due to the great interest in this class of pharmacologically active compounds, we report the preparation of novel functionalized azolopyrimidine derivatives by the reaction of ketene S,S-acetal derivatives, and with some aminoazoles in the presence (or absence) of triethylamine. These compounds show fluorescence properties and can be used as OLEDs. It also helps in preventing many viral, fungal, and bacterial disease, as well as, act as an anti-tuberculosis and antioxidant drug with low toxicity. Because of the high efficiency of these compounds following research groups have recognized the importance of this field and made substantial contributions internationally.

1) Yoshinori Tominaga
Faculty of Environmental Studies,
1-14, Bunkyo-machi,
Nagasaki 852-8521, Japan.

2) M. A. Metwally
Department of Chemistry,

Faculty of Science,
Mansoura University, Mansoura, Egypt.

3) W. Ried
Institute of Organic Chemistry,
University of Frankfurt Laboratory Niederrad.
Theodor-Stern-Kai 7.o-6000
Frankfurt am Main 70, West Germany.

- **National Status:**

Nitrogen, Sulphur, and oxygen-containing heterocycles such as pyrimidine, pyrazole, imidazole, quinoline benzothiazole, and Pyrazole have been widely used in drug molecules these compounds act as antiviral, antifungal, anti-HIV, anticancer, antioxidant, anti-inflammatory agents with low toxicity. Because of the high efficiency of these compounds, the following research groups have recognized the importance of this field and made significant contributions nationally.

1. **Dr. Akkattu T. Biju**
   Associate Professor
   Department of Organic Chemistry
   Indian Institute of Science, Bangalore-560012, India

2. **Dr. N. T. Patil**
   Associate Professor,
   Indian Institute of Science Education
   And Research, Bhopal-462066

3. **Dr. D. Srinivasa Reddy**
   Senior Principal Scientist,
   National Chemical Laboratory, Pune, India

- **Significance of the study:**

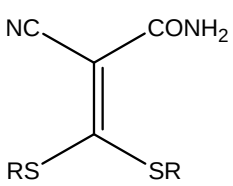
The investigation of novel antimicrobial drugs is an area characterized by vigorous exploration with the goal of overcoming the occurrence of multiple drug resistance. Fused heterocyclic rings like pyridine, pyrimidine, quinoline, thiazole, pyrazole, and benzothiazole, were found to be biologically active compounds.

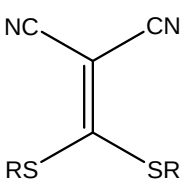
A fused hetero aromatic group containing sulfur, nitrogen, oxygen, etc atoms plays an important role as the hetero aromatic is incorporated into the structure of many pharmaceuticals.

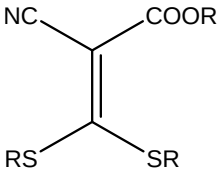
6. Proposed work plan/ Formulation and structure of study:

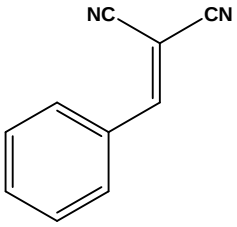
a) Synthesis of amino heterocycles and reagents: (I^{st}Year)

In the proposed research work we plan to synthesize different ketene dithioacetals and different substituted amino heterocycles containing sulfur, nitrogen, and oxygen as heteroatom.

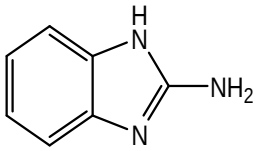




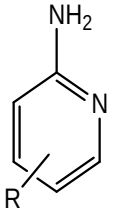




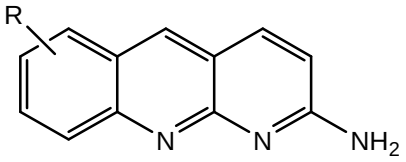
2-benzylidenemalononitrile



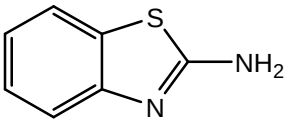
Substituted 2-Amino Benzimidazole



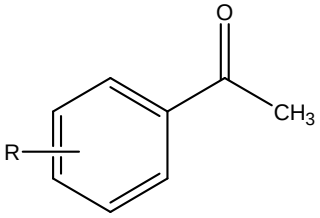
Substituted 2-amino pyridine



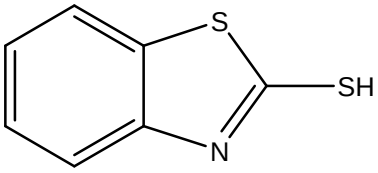
Substituted benzoquinolin-2-amine



Substituted 2-amino benzothiazole



Substituted acetophenone



Benzothiazole-2-thiol

b) Condensation of synthesized amino heterocycles with different reagents: (IInd year)

The synthesized amino heterocycles which contains more than one hetero atom as hetero atom condensation with reagents like guanidine hydrochloride, thiourea, and urea to synthesize main heterocyclic compounds.

Synthesized parent compounds treated with different substituted aniline, phenol, heteryl amine, and active methylene compound will give new heterocyclic derivatives.

The above new parent pyrimido compound condensed with a compound containing nitrogen atoms like hydrazine hydrate, Hydrazeno heterocycles, and carbonyl compounds to obtain new fused pyrazolo series derivatives.

Purification of synthesized compounds by using crystallization and conformation of the structure by using spectral data.

c) Evaluation of Physicochemical Parameters: (IIIrd Year)

The physicochemical study of heterocyclic compounds has a very wide scope as this study can demonstrate how our synthesized compounds affect physical properties such as solubility, density, viscosity, and refractive index. Study of molecular modeling of the newly synthesized compound. Molecular modeling is an efficient way of studying protein-protein interactions. It provides detailed information about how protein residues interact with each other at the atomic level. Molecular docking is a technique that predicts the preferred orientation, affinity, and interaction of a ligand in the binding site of a protein.

d) Evaluation of Biological Activity: (IIIrd Year)

The above newly synthesized compounds are to be screened for their pharmacological properties like antioxidant, antimicrobial, antimalarial, antifungal, antituberculosis, anticancer, anti-inflammatory, etc.

7. References:

1) S. V. Kuberkar and et. al. ARKIVOC 2006 (X) 190-198.
2) Sambhaji P. Vartale et.al., *J. Heterocyclic Chem*., 2013, 350,351-355.
3) M.S. Shingare,* S.A. Sadaphal et.al. Arabian Journal of Chemistry (2012) 5, 257–261.
4) Dr. S.P. Vartale and et.al. Arabian Journal of Chemistry (2012) xxx, xxx–xxx.
5) Sambhaji P. Vartale et.al., *Letters in Organic Chemistry*,2009,6(7),544-548.
6) S. V. Kuberkar and et.al. . Indian Journals of Heterocyclic chemistry Vol- 15, Jan-March, 2006, pp-275-278.
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10) Sambhaji P. Vartale *, Shivaji B. Sirsat. Heterocyclic communication (2013;19(3): 215-218.
11) Omar K. Ahmad, and Mohammad Movassaghi* Matthew D. Hill. JOC note (American chemical society) 2009, 8460-8463.
12) Mohamed A. Abdelgawad et.al. (Arabian Journal of Chemistry, Science Direct) Volume 15, Issue 8, August 2022, 104015.

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